

***Amendments to the Claims***

This listing of claims will replace all prior versions, and listings of claims in the application.

1. (currently amended) A method of diagnosing or prognosticating Alzheimer's disease in a subject, or determining whether a subject is at increased risk of developing said disease, comprising determining a level and/or an activity of
  - (i) a transcription product of ~~the~~ a gene coding for KCNE4, and/or
  - (ii) a translation product of the gene coding for KCNE4, and/or
  - (iii) a fragment, or derivative, or variant of said transcription or translation product,in a sample obtained from said subject and comparing said level and/or said activity of said transcription product and/or said translation product to a reference value representing a known disease status and/or to a reference value representing a known health status, and said level and/or said activity is varied compared to a reference value representing a known health status, and/or is similar or equal to a reference value representing a known disease status, thereby diagnosing or prognosticating Alzheimer's disease in said subject, or determining whether said subject is at increased risk of developing said disease.
2. (currently amended) A kit for diagnosing or prognosticating a neurodegenerative disease[[,]] ~~in particular Alzheimer's disease~~[[,]] in a subject, or determining the propensity or predisposition of a subject to develop such a disease, said kit comprising at least one reagent which is selected from the group consisting of

- (i) reagents that selectively detect a transcription product of ~~the~~ a gene coding for KCNE4 protein and
- (ii) reagents that selectively detect a translation product of the gene coding for KCNE4 protein,

whereby the diagnosis or prognosis or determination of the propensity or predisposition to develop ~~Alzheimer's disease~~ said neurodegenerative disease is determined by the steps of

[[~~(i)~~]] (a) detecting in a sample obtained from said subject a level, or an activity, or both said level and said activity of a transcription product and/or of a translation product of a gene coding for KCNE4, and

[[~~(ii)~~]] (b) comparing said level or activity, or both said level and said activity of a transcription product and/or of a translation product of a gene coding for KCNE4 to a reference value representing a known health status and/or to a reference value representing a known disease status, and said level, or activity, or both said level and said activity, of said transcription product and/or said translation product is varied compared to a reference value representing a known health status, and/or is similar or equal to a reference value representing a known disease status.

3. (currently amended) A modulator of an activity and/or of a level of at least one substance which is selected from the group consisting of
- (i) a gene coding for KCNE4 protein, ~~and/or~~
  - (ii) a transcription product of the gene coding for KCNE4 protein, ~~and/or~~

- (iii) a translation product of the gene coding for KCNE4 protein, ~~and/or~~ and
  - (iv) a fragment, or derivative, or variant of (i) to (iii).
4. (original) A recombinant, non-human animal comprising a non-native gene sequence coding for KCNE4 or a fragment, or a derivative, or a variant thereof, said animal being obtainable by:
- (i) providing a gene targeting construct comprising said gene sequence and a selectable marker sequence, and
  - (ii) introducing said targeting construct into a stem cell of a non-human animal, and
  - (iii) introducing said non-human animal stem cell into a non-human embryo, and
  - (iv) transplanting said embryo into a pseudopregnant non-human animal, and
  - (v) allowing said embryo to develop to term, and
  - (vi) identifying a genetically altered non-human animal whose genome comprises a modification of said gene sequence in both alleles, and
  - (vii) breeding the genetically altered non-human animal of step (vi) to obtain a genetically altered non-human animal whose genome comprises a modification of said endogenous gene, wherein said disruption results in said non-human animal exhibiting a predisposition to developing symptoms of a neurodegenerative disease or related diseases or disorders.
5. (currently amended) ~~Use of~~ A method of developing diagnostics and therapeutics to treat neurodegenerative diseases, comprising screening, testing, or validating compounds, agents, or modulators using the recombinant, non-human

animal according to claim 4 ~~for screening, testing, and validating compounds, agents, and modulators in the development of diagnostics and therapeutics to treat neurodegenerative diseases, in particular Alzheimer's disease.~~

6. (currently amended) ~~An assay~~ A method for screening for a modulator of neurodegenerative diseases, ~~in particular Alzheimer's disease~~[[,]] or related diseases or disorders of one or more substances selected from the group consisting of

- (i) a gene coding for KCNE4 protein, ~~and/or~~
- (ii) a transcription product of the gene coding for KCNE4 protein, ~~and/or~~
- (iii) a translation product of the gene coding for KCNE4 protein, ~~and/or~~ and
- (iv) a fragment, or derivative, or variant of (i) to (iii),

said method comprising:

- (a) contacting a cell with a test compound;
- (b) measuring the activity and/or level of one or more substances recited in (i) to (iv);
- (c) measuring the activity and/or level of one or more substances recited in (i) to (iv) in a control cell not contacted with said test compound; and
- (d) comparing the levels and/or activities of the substance in the cells of step (b) and (c), wherein an alteration in the activity and/or level of substances in the contacted cells indicates that the test compound is a modulator of said diseases or disorders.

7. (currently amended) A method of screening for a modulator of neurodegenerative diseases, ~~in particular Alzheimer's disease~~[[,]] or related

diseases or disorders of one or more substances selected from the group consisting of

- (i) a gene coding for KCNE4 protein, ~~and/or~~
- (ii) a transcription product of the gene coding for KCNE4 protein, ~~and/or~~
- (iii) a translation product of the gene coding for KCNE4 protein, ~~and/or~~ and
- (v) a fragment, or derivative, or variant of (i) to (iii),

said method comprising:

- (a) administering a test compound to a test animal which is predisposed to developing or has already developed symptoms of a neurodegenerative disease or related diseases or disorders in respect of the substances recited in (i) to (iv);
- (b) measuring the activity and/or level of one or more substances recited in (i) to (iv);
- (c) measuring the activity and/or level of one or more substances recited in (i) or (iv) in a matched control animal which is predisposed to developing or has already developed symptoms of a neurodegenerative disease or related diseases or disorders in respect to the substances recited in (i) to (iv) and to which animal no such test compound has been administered;
- (d) comparing the activity and/or level of the substance in the animals of step (b) and (c), wherein an alteration in the activity and/or level of substances in the test animal indicates that the test compound is a modulator of said diseases or disorders.

8. (original) The method according to claim 7 wherein said test animal and/or said control animal is a recombinant animal which expresses KCNE4, or a fragment, or a derivative, or a variant thereof, under the control of a transcriptional control element which is not the native KCNE4 gene transcriptional control element.
9. (currently amended) An assay for testing a compound, ~~preferably for screening~~ or a plurality of compounds to determine the degree of binding of said compounds to KCNE4 protein, or to a fragment, or derivative, or variant thereof, said assay comprising the steps of:
  - (i) adding a liquid suspension of said KCNE4 protein, or a fragment, or derivative, or variant thereof, to a plurality of containers;
  - (ii) adding a detectable[[,]] ~~in particular a fluorescently labelled~~ compound or a plurality of detectable[[,]] ~~in particular fluorescently labelled~~ compounds to be screened for said binding to said plurality of containers;
  - (iii) incubating said KCNE4 protein, or said fragment, or derivative, or variant thereof, and said detectable[[,]] ~~in particular fluorescently labelled~~ compound or ~~detectable, in particular fluorescently labelled~~ compounds;
  - (iv) measuring amounts of ~~preferably the fluorescence~~ detectable compound or compounds associated with said KCNE4 protein, or with said fragment, or derivative, or variant thereof; and
  - (v) determining the degree of binding by one or more of said compounds to said KCNE4 protein, or said fragment, or derivative, or variant thereof.
10. (currently amended) ~~Use of~~ The method of claim 1, comprising determining a level and/or an activity of a protein molecule of SEQ ID NO. 1, said protein



molecule being a translation product of the gene coding for KCNE4, or a fragment, or derivative, or variant thereof[[,]] ~~as diagnostic target for detecting a neurodegenerative disease, preferably Alzheimer's disease.~~

11. (currently amended) ~~Use of~~ The method of claim 6, wherein said screening is for a modulator of a protein molecule of SEQ ID NO. 1, said protein molecule being a translation product of the gene coding for KCNE4, or a fragment, or derivative, or variant thereof, wherein said modulator is a reagent or compound ~~for as screening target for reagents or compounds preventing, or treating, or ameliorating a neurodegenerative disease[[,]] preferably Alzheimer's disease.~~
12. (currently amended) ~~Use of~~ A method for detecting the pathological state of a cell in a sample obtained from a subject, comprising immunocytochemical staining of said cell with an antibody specifically immunoreactive with an immunogen, wherein said immunogen is a translation product of a gene coding for KCNE4, SEQ ID NO. 1, or a fragment, or derivative, or variant thereof, for ~~detecting the pathological state of a cell in a sample obtained from a subject, comprising immunocytochemical staining of said cell with said antibody,~~ wherein an altered degree of staining, or an altered staining pattern in said cell compared to a cell representing a known health status indicates a pathological state of said cell which relates to Alzheimer's disease.
13. (new) The kit of claim 2, wherein said neurodegenerative disease is Alzheimer's disease.
14. (new) The kit of claim 2, wherein said translation product is a protein molecule of SEQ ID NO. 1, said protein molecule being a translation product of the gene coding for KCNE4, or a fragment, or derivative, or variant thereof.
15. (new) The recombinant, non-human animal of claim 4, wherein said neurodegenerative disease is Alzheimer's disease.

16. (new) The method of claim 6, wherein said neurodegenerative disease is Alzheimer's disease.
17. (new) The method of claim 7, wherein said neurodegenerative disease is Alzheimer's disease.
18. (new) The method of claim 7, wherein said screening is for a modulator of a protein molecule of SEQ ID NO. 1, said protein molecule being a translation product of the gene coding for KCNE4, or a fragment, or derivative, or variant thereof, wherein said modulator is a reagent or compound for preventing, or treating, or ameliorating a neurodegenerative disease.
19. (new) The assay of claim 9, wherein said detectable compound is a fluorescently labeled compound.